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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT
CINCINNATI, OH 45268

OFFICE OF
RESEARCH AND DEVELOPMENT

October 23, 1995

Mr. Mike Girrard
Chairman
Perchlorate Study Group

Dear Mr. Girrard:

Enclosed is NCEA's conclusions regarding the perchlorate provisional RfD based on our review of the report submitted by the Perchlorate Study Group in June 1995. To summarize, there are many questions about the chronic effects of perchlorate left unanswered by the existing data. The series of studies that identified a human Frank Effects Level at doses ranging from 6-14 mg/kg/day is particularly troubling. Thus, until adequate chronic data is available that addresses the effects of perchlorate on the hematopoietic system, we feel that the appropriate provisional RfD is in the range of 1 to 5E-4 mg/kg/day.

Sincerely yours,

Joan S. Dollarhide

Enclosure

Review of Proposed RfD for Perchlorate

In June 1995, the Perchlorate Study Group (PSG) submitted to NCEA-Cincinnati a report evaluating the literature on perchlorate compounds and proposing a new provisional RfD to be used by the Superfund Technical Support Center while additional data on perchlorates are being generated. This review comments on the different elements of the proposed RfD and recommends alternative approaches.

Quality of Database

As the PSG report notes, there is an abundance of studies on perchlorate. The attached table provides a summary of the existing data. Unfortunately, most of the studies are of limited value in developing a chronic RfD. Because perchlorate had been used as a treatment for Graves disease, many studies in hyperthyroid patients exist. Only two studies [Burgi (1974) and Brabant (1992, 1994)] evaluated perchlorate in healthy subjects. The PSG report cites Shigan (1963) as evaluating perchlorate in humans; however, the translation which NCEA reviewed did not include a study in humans. If there is another Shigan (1963), we were not able to locate it. Except for Connell (1981) which reports on one subject treated for 22 years, all of the human studies are less than chronic, ranging in length from a single dose to 6 months. Only Stanbury and Wyngaarden (1952) identified a NOAEL, 0.14 mg/kg/day based on release of iodine from the thyroid and inhibition of iodine uptake by the thyroid. Connell (1981) reported no side effects in one patient treated with 3 mg/kg/day perchlorate for 22 years. However, since this dose was effectively controlling the clinical signs of hyperthyroidism, it seems reasonable to assume that this dose was having an effect on the thyroid. Based on the body of human studies, it appears that perchlorate doses above 1.4 mg/kg/day have adverse effects on the thyroid. Doses in the range of 6-14 mg/kg/day appear to cause fatal bone marrow effects in subjects treated for 2 months or longer, making this dose range a Frank Effect Level (FEL).

Several animal bioassays have been conducted ranging in length from 4 days (Mannisto, 1978) to two years (Kessler and Kruskemper, 1966). For the most part, all of these studies are limited by the fact that the doses tested were not at levels low enough to identify NOAELs and that no organs, tissues, or endpoints other than thyroid were examined. The exception to this statement is Shigan (1963) which identified a NOAEL at 0.25 mg/kg/day and a LOAEL at 2 mg/kg/day. This study appeared to examine cardiac electrical activity, liver function, and conditioned reflexes in addition to thyroid function. However, this study is not reported and/or translated well enough to be useful for risk assessment. Mannisto (1978) also identified a NOAEL (1.5 mg/kg/day) and LOAEL (7.6 mg/kg/day) based on thyroid effects but this study is limited by its short duration and lack of other endpoints evaluated. Three studies treated dams during gestation; limited developmental endpoints were examined. In addition, there are no reproductive or multigeneraltional studies.

In summary, the studies by Brabant and the cluster of studies showing fatal aplastic anemia clearly show that the duration of exposure affects response. Thus, the database for perchlorate is severely limited by the fact that there is no chronic study which is conducted at

levels low enough to demonstrate a NOAEL and which examines the full range of potential toxicities.

Critical Study and Effect

The PSG report proposes the Brabant studies as the critical studies on which to base the RfD. Obviously, risk assessments based on human data have the advantage of avoiding the problems inherent in interspecies extrapolation. However, the Brabant studies have limitations which limit their usefulness for risk assessment. Brabant (1992) pretreated healthy volunteers with iodine for four weeks prior to treatment with perchlorate. As the PSG report notes, Brabant (1992) observed a decrease in TSH levels. The authors question whether this decrease is related to the iodine supplementation. Thus, before this study could be used in a risk assessment, more information would be needed on the effects of iodine pretreatment on the mechanism of perchlorate action.

EPA has defined "critical effect" as the effect exhibiting the lowest LOAEL. Applying this definition to the perchlorate database, it appears that interference with the thyroid (including release of iodine from the thyroid, inhibition of iodine uptake by the thyroid, increased thyroid weight and volume, increased TSH levels and decreased T3/T4 levels) is the critical effect for perchlorate. However, no other studies, except Shigan (1963), even looked for effects other than thyroid. Given that several human studies show fatal bone marrow effects at the same dose levels at which thyroid effects are observed, it is possible that subtler bone marrow toxicity would be observed at even lower doses. Thus, without additional data, it is difficult to state with certainty that the critical effect has been identified.

In addition, the PSG report approaches definition of critical effect in a way that is not consistent with EPA's approach. The PSG report first defines the critical effect (in this case statistically significant increase in TSH and decrease in T3/T4) and then finds the studies that demonstrate the effect. This is not appropriate.

Choice of NOAEL/LOAEL

In selecting a dose level as the basis for the RfD, the approach is to select the dose level that represents the highest level tested in which no adverse effects were observed. When examining an entire database, practically, this means that the highest NOAEL which is lower than the lowest LOAEL is the dose level used as the basis for the RfD. The PSG report recommends the 12 mg/kg/day dose from the Brabant studies as the basis for the RfD. This is not an appropriate choice for several reasons. Based on the effects observed in Brabant (1992) of decreased thyroid iodine concentration, decreased free T4, and decreased thyroglobulin, the dose of 12 mg/kg/day is a LOAEL. This is supported by Brabant's follow up studies which observed increased thyroid volume at the same dose after just one additional week of exposure. Thus use of this dose is inappropriate because several studies reported effects at lower doses (LOAELs of 1.4 mg/kg/day in Stanbury and Wyngaarden (1952), 2 mg/kg/day in Shigan (1963), 7.6 mg/kg/day

in Mannisto (1978)). In addition, use of the 12 mg/kg/day dose is not appropriate because this dose is higher than doses which have resulted in human deaths from aplastic anemia resulting from perchlorate exposure. The PSG report states that "all known toxicities of perchlorate to other target organs such as the ... hematopoietic system are probably mediated by thyrotoxicity", but provides no scientific evidence to support this statement. None of the papers reviewed for this report address this issue, and I was not able to find evidence to support this statement after a limited search through the literature. Before we can disregard the effect of perchlorates on the bone marrow for risk assessment purposes, there needs to be much stronger evidence that the thyroid effects and bone marrow effects are directly linked.

Uncertainty Factors

The PSG report states that the only uncertainty factor needed is a factor of three to accound for sensitive subpopulations. This is not consistent with EPA's approach. An uncertainty factor accounting for extrapolation from less than lifetime studies would be required because all of the studies which identified NOAELs are acute or subchronic studies. An uncertainty factor for database deficiencies is required to account for data limitations including limited data on subchronic and chronic exposure to *low* doses of perchlorate, limited data on other organ systems, limited data on the effects on the hematopoietic system, and lack of reproductive and multigenerational data. A full uncertainty factor of 10 should be considered to protect sensitive subpopulations which would include groups not considered in the PSG report such as hypothyroid patients and individuals with low iodine diets or with genetically impaired iodine accumulation.

Recommendations

ECAO's original assessment of perchlorate resulted in an RfD of 1E-4 mg/kg/day based on a NOAEL of 0.14 mg/kg/day in Stanbury and Wyngaard (1952) and an uncertainty factor of 1000. After a thorough review of the PSG report and all of the studies currently in the perchlorate database, NCEA believes that this value is reasonable as a provisional value to be used in the interim while additional data are being collected. Until we understand more about the effects of *chronic* exposure and understand more about the relationship between perchlorate exposure and the hematopoietic system, it would be irresponsible to base an RfD on any of the studies which identified LOAELs greater than or equal to 6 mg/kg/day.

A provisional RfD in the order of 1E-4 is supported by the other studies which identified NOAELs. For example using the NOAEL 0.25 mg/kg/day from Shigan (1963), the uncertainty factors would be 3000 (10 each for inter and intraspecies extrapolation, 10 for database, and 3 for less than lifetime) and the provisional RfD would be 1E-4 mg/kg/day. Using the NOAEL of 1.5 mg/kg/day from Mannisto (1978), the uncertainty factor would be 10,000 (a full 10 for four areas of uncertainty including inter and intraspecies extrapolation, database, and use of acute data) and the RfD would be 2E-4 mg/kg/day. There was some discussion that a full 10 for database deficiencies may not be required. Applying a 3 instead of 10 to the above estimates has the following results: Stanbury and Wyngaard (1952), NOAEL 0.14, UF 300, RfD 5E-4 mg/kg/day;

Shigan (1963), NOAEL 0.25, UF 1,000, RfD 3E-4 mgkgday; Mannisto (1978), NOAEL 1.5, UF 3,000, RfD 5E-4 mg/kg/day. Thus, until new data is available to resolve the issues described above, the appropriate provisional RfD for perchlorate appears to be in the range of 1 to 5E-4 mg/kg/day.

Study	Species (n)	Duration	Doses (mg/kg/day)	Effects	Notes
Human Studies					
Stanbury and Wyngaarden (1952)	Human (3)	single dose	0 0.04 0.14 N 1.4 L	Release of iodine from thyroid. Inhibition of iodine uptake by thyroid	Graves disease patients
Burgi et al (1974)	Human (5)	8 days	0 9.7 L	Release of iodine from thyroid	Healthy volunteers
Godley and Stanbury (1954)	Human (24)	28 weeks	0 8.6 L	Gastrooointestinal irritation in 2/24 patients. ↓ of iodine uptake by thyroid	Graves disease patients
Cooks and Wayne (1960)	Human (35) (165) (10) (40)	unknown	8.6 L 14 21 28	Skin rash, nausea at 8.6-14. Above plus agranulocytosis at 21	Graves disease patients
Morgan and Trotter (1960)	Human (180) (67)	2-3 weeks	6-14 L 17-28	Skin rash, sore throat, GI irritation, lymphadenopathy(3% in low dose 18% in high dose)	Graves disease patients

Study	Species (n)	Duration	Doses (mg/kg/day)	Effects	Notes
Animal Studies					
Kessler and Kruskemper (1966)	Male Wistar Rats (6-8/group)	2 years	0 (water) 1339 L	↑ absolute and relative thyroid weight. Follicular cell hyperplasia	No other tissues examined
Pajer and Kalisnik (1991)	Female Balb/c mice (36/group)	46 weeks	0 (water) 2147 L	↑ thyroid volume, pituitary TSH; histopathological changes in thyroid; follicular cell carcinoma	No other tissues or organ systems examined
Shigan (1963)	Rabbits, Rats (#, sex not specified)	9 months	0 (water?) 0.25 N 2 L 40	↑ secretion of Iodne from thyroid; no effects on other organs	The only other effects tested for are cardiac electrical activity, liver function, conditioned reflexes
	Rabbits, Rats (#, sex not specified)	3 months	0 (water) 190 L	Changes in cardiac electrical activity and liver function	Study not well enough reported/translated to be useful for risk assessment
Gauss (1972)	Female NMRI mice	160 days	0 (diet) 2011 L	↑ thyroid volume and histological changes to thyroid	

Study	Species (n)	Duration	Doses (mg/kg/day)	Effects	Notes
Brabant et al. (1992)	Human (5)	4 weeks	12 L	↑ thyroid iodide conc, free T4, thyroglobulin, TSH	Healthy volunteers pretreated with iodine for 4 weeks before exposure, resulting in ↑ TSH. Follow-up studies show ↑ thyroid volume at same dose
Connell (1981)	Human (1)	22 years	3 N	No adverse effects observed with clinical control of hyperthyroidism	
Hobson (1961)	Human (1)	33 weeks	9-11 F	Fatal aplastic anemia	
Johnson and Moore (1961)	Human (1)	3 months 1 month	14 F 9	Fatal aplastic anemia	
Fawcett and Clark (1961)	Human (1)	6 months 2 months	9 F 6	Fatal aplastic anemia	
Krevans et al (1962)	Human (1)	2 weeks 10 weeks 4 months	11 9 6 F	Fatal aplastic anemia	
Gjemdal (1963)	Human (1)	4 months	6-9 F	Fatal aplastic anemia	
Barzilai and Sheinfeld (1966)	Human (2)	2 months	14 F	Fatal aplastic anemia and fatal agranulocytosis	

Study	Species (n)	Duration	Doses (mg/kg/day)	Effects	Notes
Hiasa et al. (1987)	Male Wistar Rats (20/group)	20 weeks	0 (diet) 81 L	↑ absolute and relative thyroid weight, serum TSH. ↓ serum T4	No effect on body or liver weight. No other parameters examined. No histopathology.
Mannisto et al (1978)	Male Sprague-Dawley Rats (5-6/group)	4 days	0 (water) 1.5 N 7.6 L 15.3 76.3	↑ TSH ↓T3/T4	No other endpoints examined. No histopathology.
Brown-Grant (1966)	Female Wistar Rats (11/group)	gestation day 2-8	0 (water) 63 246	None	Developmental effects and maternal toxicity not evaluated. Only endpoint examined was # live litters.
Brown-Grant and Sherwood (1971)	Female Wistar Rats (10/group)	gestation day 0 to day 12/13	1% in water L	↓ dams with implantation sites, ↑ maternal and pup thyroid weight	no untreated controls
Postel (1957)	Female guinea pigs	gestation day 21-48	0 (water) 740 L	↑ fetal thyroid weight	Fetuses were not examined for other developmental effects.